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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/010,377 | 01/21/1998 | S.A. RUBIN | 015270-00430 | 8602 |

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| EXAMINER | |
|---|---|
| GAMBEL, PHILLIP | |
| ART UNIT | PAPER NUMBER |
| 1644 | 32 |

DATE MAILED: 03/11/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) |
|---|---|---|
| | 09/ 010377 | RUBIN |
| | Examiner | Art Unit |
| | GAMBEL | 1644 |

– The MAILING DATE of this communication appears on the cover sheet with the correspondence address –

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☑ Responsive to communication(s) filed on 12/30/03

2a)☑ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☑ Claim(s) _____ is/are pending in the application. 1-18, 20-22

4a) Of the above claim(s) _____ is/are withdrawn from consideratio 21, 22

5)☐ Claim(s) _____ is/are allowed.

6)☑ Claim(s) _____ is/are rejected. 1-18, 20

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requireme

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☑ The drawing(s) filed on 12/30/03 is/are: a)☑ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disappr d by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1)☐ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4)☐ Interview Summary (PTO-413) Paper No(s). _____.
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other:



PAPER NO. 32

## DETAILED ACTION

1. Applicant's amendment, filed 12/30/02 (Paper No. 30), has been entered.
Claim 19 has been canceled.
Claims 20-22 have been added.

Claims 1-18 and 20-22 are pending.

Newly submitted claims 21-22 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: Newly submitted claims 21-22 are drawn to agents comprising peptides and peptides derivatives, including peptides set forth in SEQ ID NOS: 3-5 in the claimed methods of treating viral encephalitis previously not claimed explicitly. Claims 21-22 are drawn to the use of agents which differ in structure and modes of actions from the anti-VLA-4 / anti alpha-4 antibodies prosecuted in the instant application.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 21-22 are withdrawn from consideration as being directed to a non-elected invention. See 37 C.F.R. § 1.142(b) and M.P.E.P. § 821.03.

Claims 1-18 and 20 are under consideration in the instant application.

2. The text of those sections of Title 35 USC not included in this Action can be found in a prior Action.
This Office Action will be in response to applicant's arguments, filed 12/30/02 (Paper No. 30).
The rejections of record can be found in the previous Office Actions (Paper Nos. 9/12/17/28).

Applicant's arguments and the examiner's rebuttal are essentially the same as of record.

3. Formal drawings submitted 12/30/02 (Paper No. 31) comply with 37 CFR 1.84.

4. Claims 1-8, 11, 14-18 (and non-elected claim 21) are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of treating viral encephalitis with "antibodies that bind the alpha-4 subunit of VLA-4" and peptides having the formula set forth in SEQ ID NOS: 3/4/5 as disclosed on pages-10 of the instant specification, does not reasonably provide enablement for any "agent that inhibits binding of leukocytes to brain endothelial cells via leukocyte surface antigen alpha-4 integrin". The specification does not enable any person skilled in the art to which it pertains, or with which it is most clearly connected, to make and use the invention commensurate in scope with these claims.

Applicant's arguments, filed 12/30/02 (Paper No. 30), have been fully considered but are not found convincing essentially for the reasons of record.

Applicant's arguments, filed 12/30/02 (Paper No. 30) and the examiner's rebuttal are essentially the same of record.

Applicant asserts that the specification does teach how to find and screen various agents, including antibodies, peptides and small molecules, for the requisite ability to inhibit binding of leukocytes to brain endothelial cells via leukocyte surface antigen alpha-4 integrin.

As applicant acknowledges, the specification provides for methods to test for other potential therapeutic agents for the appropriate binding specificity and/or the capacity to block the interaction of VLA-4 with inflamed endothelial cells, VCAM-1 expressing cells or purified VCAM-1.

Therefore, in providing a description on how to conduct screening assays, the specification essentially calls for the use of trial and error to attempt to find a compound that has the requisite ability to inhibit binding of leukocytes to brain endothelial cells via leukocyte surface antigen alpha-4 integrin. There is insufficient guidance in the way of selecting a particular compound or narrowing the range of candidates in order to find a suitable compound without the need of undue experimentation, other than "antibodies that bind the alpha-4 subunit of VLA-4" and peptides having the formula set forth in SEQ ID NOS: 3/4/5 as disclosed on pages-10 of the instant specification and known in the prior art. The instant application provides for assays for identifying agents which possess certain desired characteristics and identifies certain broad categories of agents that might work amounts to a starting pont or a direction for further research. The specification does not provide sufficient guidance or specificity as to execute the plan or invitation for the skilled artisan to experiment practicing the invention, encompassed by the scope of the claimed agents employed in the claimed methods.

Applicant has argued that pages 9-10 and 15 provides for agents that specifically inhibit VCAM-1 binding to the $\alpha 4$ subunit of VLA-4.

As pointed out previously, the disclosure of particular peptides having the formula set forth in SEQ ID NOS: 3/4/5 as set forth on pages 9-10 of the instant specification; such peptides are considered enabled.
It is noted that these peptides disclosed in WO 96/01644.
Again, applicant should recite these peptides in the claims.

Applicant asserts that the reliance on the disclosure of other peptides disclosed in WO 96/22966; WO 96/20216; WO 96/00581 and WO 9606108 does not constitute essential subject matter. In addition to the reliance on the identification of certain agents disclosed in the specification, applicant submits that other reagents can be identified by various routine methods and well within the purview of the skilled artisan. Such assertions are not found convincing for the reasons of record and that set forth herein.

Also, applicant's comments that the claims are drawn to methods and not directed to specific agents are not found convincing in that the claimed methods rely upon specific agents in order to treat viral

encephalitis. Similarly,, applicant's submission that the identify of the agents are not essential materials does not comport with the ability to make and use agents to treat viral encephalitis, as encompassed by the claimed methods.

Again, applicant appears to rely upon the disclosure of other peptides disclosed in WO 96.22966; WO 96/20216; WO 96/00581 and WO 9606108 as well as U.S. Patent No. 5,510,332 (1449; #AB).

Here, it appears applicant is attempting to incorporate by reference essential subject matter to non-U.S. Patents.

In contrast to relying upon either SEQ ID NOS: 3/4/5 or U.S. Patent No. 5,510,332 which are disclosed in the instant specification as filed; applicant is attempting to incorporate by reference essential subject matter either to non-U.S. Patents or to material not disclosed in the application as filed.

A more thorough review of applicant's arguments and the examiner's rebuttal of record can be found in Paper No. 28.

Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. Without sufficient guidance, the changes which can be made in the structure of "any agent that inhibits binding of leukocytes to brain endothelial cells via leukocyte surface antigen alpha-4 integrin"or "that specifically bind the alpha-4 subunit of VLA-4", and still provide or maintain sufficient activity to treat viral encephalitis would be unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue

Again, applicant is invited to recite the particular peptides having the formula set forth in SEQ ID NOS: 3/4/5 as set forth on pages 9-10 of the instant specification into the claimed methods.

Otherwise, applicant's arguments have been fully considered but are not found convincing essentially for the reasons of record, as the claims read on any agent that inhibits binding of leukocytes to brain endothelial cells via leukocyte surface antigen alpha-4 integrin.

Applicant's arguments have not been found persuasive with the breadth of "agents that inhibit binding of leukocytes to brain endothelial cells via leukocyte surface antigen alpha-4 integrin.

5. The cancellation of claim 19 has obviated the previous rejection under 35 U.S.C. § 112, second paragraph.

6. Claims 1-18 and newly added claim 20 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Bendig et al. (U.S. Patent No. 5,840,299) AND/OR Soilu-Hanninen et al. (Scand. J. Immunol. 43: 727, 1996) AND/OR Soilu-Hanninen et al. (J. Neuroimmunol. 72: 95-105; 1997; 1449) and further in view of Ashwell et al. (U.S. Patent No. 6,291,453) essentially for the reasons of record set forth in Paper No. 28.

Claims 1-18 and newly added claims 20 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Bendig et al. (U.S. Patent No. 5,840,299) AND/OR Soilu-Hanninen et al. (Scand. J. Immunol. 43: 727, 1996) AND/OR Soilu-Hanninen et al. (J. Neuroimmunol. 72: 95-105; 1997; 1449) and further in view of Ashwell et al. (U.S. Patent No. 6,291,453)., as applied to claims 1-19 above
and in further view of the art known role or etiology of various viruses inducing encephalitis, as evidenced by Planz et al. (J. Virol. 69: 896-903, 1995; 1449)
AND/OR
the role herpes viruses in multiple sclerosis, as taught by Sanders et al. (Archives of Neurology 53: 125-133, 1996) AND/OR Editorial (Archives of Neurology, 53: 123-124, 1996) essentially for the reasons of record set forth in Paper No. 28.

Applicant's arguments, filed 12/30/02 (Paper No. 30), have been fully considered but are not found convincing essentially for the reasons of record.

Applicant's arguments, filed 12/30/02 (Paper No. 30) and the examiner's rebuttal are essentially the same of record.

Applicant submits certain references, including
Gilden, JAMA 286 : Editorial (2001);
Taus et al., Acta Neurol. Scand. 101: 224-228 (2000);
Martin et al., Acta Neurol. Scand. 95: 280283 (1997); and
Simmons, Herpes 8: 60-63 (2001)
to indicate that there was no relationship between herpesviruses an multiple sclerosis and any association between herpesviruses and multiple sclerosis remains controversial and inconclusive at best.

Again, applicant submits with the Karlik Declaration, filed under 37 C.F.R. § 1.132, filed 12/5/01 (Paper No. 24), that the animal models disclosed in the present application is different from the models discussed in the cited art, the animals models discussed in the cited art are not predictive of the efficacy of anti-VLA-4 agents in viral encephalitis in the absence of multiple sclerosis and the animal model of the subject application is predictive that agents to VLA-4 are useful in treating simple viral encephalitis.

Karlik pointed out that the animal models of the cited references rely upon the effects of anti-$\alpha$4 in inhibiting inflammation due to EAE, a syndrome simulating multiple sclerosis. Also, this model simulates autoimmune diseases which does not result from viral sources. Karlik noted that viral inflammation could not have been addressed in the EAE model of Bendig et al. And that the results of the EAE models do not directly address the ability of anti-$\alpha$4 antibodies to treat inflammation due exclusively to viral infection.

Karlik pointed out that the present inventors employed an animal model in which inflammation is solely the result of viral infection, wherein the results indicate that treatment with anti-α4 antibodies is effective in suppressing the harmful effects that keep viral replication in check without significantly suppressing the beneficial effects that keep viral replication in check. For example, treating with anti-α4 antibodies was effective in prevent or ameliorating immune-mediated CNS damage following viral encephalitis in rats (pages 23-27) and that despite blocking the immunopathological immune response to viral encephalitis the treatment did not cause enhanced viral replication (pages 27-28). .

Karlik stated that the combination of the beneficial and harmful consequences of viral infection-induced inflammation create uncertainty in the predictability of the immunosuppressive agents that would be useful in inhibiting such inflammation. For example, if treatment with an immunosuppressive agent increased the extent of viral infection as a result of decreased immune surveillance, the agent could effectively cause an increase in the damage to the subject.

Applicant argues that since inflammatory responses are desirable to clearing viral infection, those skilled in the art would not be motivated to use agents that block the inflammatory response.

Applicant argues that Bendig fails to teach a method of treating herpesviruses infected patients that are free of multiple sclerosis using agents that inhibit the binding of alpha-4; that Soilu-Hannien (1996) and Soilu-Hanninen (1997) do not discuss treatment of herpesvirus infected patients that are free of multiple sclerosis.

In addition, applicant asserts that Semliki Forest virus is an alphavirus and not a herpesvirus, as required in the claims.
However, not all of the claims are limited to herpesviruses.

Applicant's statements concerning the distinction between EAE models / multiple sclerosis and viral encephalitis are acknowledged.

While applicant acknowledges that Ashwell teach inhibitors for VLA-4:VCAM-1 interactions, including those that bind VLA-4 are useful to treat inflammatory brain disorders, such as multiple sclerosis, viral meningitis and encephalitis, applicant asserts that Ashwell does not specifically address herpesvirus infection.

Applicant asserts that the motivation provide by Planz, Sander and the Editorial of record for motivation is countered by the teachings of submitted Gilden, Taus, Martin and Simmons.

The following of record is reiterated for applicant's convenience.

While it is noted that the claimed methods are distinguished from multiple sclerosis; it appears the combined teachings are consistent with the role of T cells in viral inflammation encompassing viral encephalitis and that there was sufficient motivation and expectation of success in inhibiting T cells via blocking VLA-4:VCAM-1 interactions to treat said viral inflammatory conditions wherein T cells contribute to the inflammation at the time the invention was made.

Again, it is noted that newly added Ashwell et al. (U.S. Patent No. 6,291,453) teaches that inhibitors for VLA-4:VCAM-1 interactions, including those inhibitors that bind α4 are useful to treat inflammatory brain disorders, such as multiple sclerosis, viral meningitis and encephalitis. Therefore, Ashwell et al. provides for treating various inflammatory brain disorders, including viral encephalitis. Also, the prior art is not limited to treating multiple sclerosis only as the brain inflammatory disorder.

As pointed out previously, Bendig et al. teach using VLA-4α-specific antibodies, including the 21.6 specificity to treat encephalitis (see entire document, including VII. Methods of Treatment on columns 14-16) treating encephalitis and multiple sclerosis).

Also, as pointed out previously; Soilu-Hanninen et al. teach using VLA-4α-specific antibodies to treat virus-facilitated EAE, including its implications relapses triggered by viral infections in multiple sclerosis and by arboviruses (see entire documents). Soilu-Hanninen et al teach that viral infections serve as triggers of relapse phases of multiple sclerosis and the relationship of viral infection with the facilitation of leukocyte entry into the CNS (see entire document, including the Abstract, Introduction and Discussion, 1997).

In contrast to applicant's arguments on lack of predictability; Planz et al. teach the role of T cell subsets in Borna disease virus induce progressive encephalitis (see entire document).

Also, it is noted Planz et al. Borna virus disease after cyclophosphamide-induced immunosuppression were treated with antibodies directed to T cells (anti-CD8 antibodies) developed neither encephalitis nor disease (see entire document, including the Abstract). Planz et al. state that the presence of $CD8^+$ T cell apparently correlated with the development of neurological symptoms (see Abstract and Discussion).

Therefore, the prior art provided an expectation of success in blocking T cells wherein the treated individuals developed neither encephalitis nor disease. Even though the anti-CD8 antibodies target cells involved in the immune response, the further treatment of anti-CD8 antibodies did not exacerbate the Borna virus disease, given the role of T cells in the development of neurological symptoms associated with virus-induced progressive encephalitis.

Also, both Archives of Neurology citations disclosed that herpes is a common neurotropic virus which was present in more multiple sclerosis patients than control cases (see entire documents).

In contrast to applicant's apparent assertions that herpesvirus infections would have to be implicated in multiple sclerosis to support the prior art rejections, the prior art provides sufficient motivation and expectation of success in treating viral infections associated with viral encephalitis, regardless of the role of herpesviruses in multiple sclerosis itself.

In contrast to applicant's assertions of the rejection is based upon an "obvious-to-try" standard; it is by now well understood that the ultimate conclusion of law that claimed subject matter as a whole would have been obvious under 35 USC 103 may at times properly be drawn from an inference of fact arising from prior art teachings which could be considered an inference that it would be "obvious to try" that which is claimed. In re O'Farrell, 853 F.2d 894, 7 USPQ 2d 1973 (Fed. Cir. 1988); Contour Saws Inc. v. Starrett Co., 444 F. 2d 433, 170 USPQ 433 (Ct.App. 1977); In re Marzocchi, 439 F. 2d 220, 169 USPQ 367 (CCPA 1977); In re Lindell, 385 F. 2d 435, 155 USPQ 521 (CCPA 1967). The evidence of purported unobvious results of record in this application is insufficient to overcome the inference of fact in this case. Therefore the above claims remain rejected under 35 USC 103 for the reasons above and also those set forth in the previous Office action.

Therefore, given the clear teaching of treating encephalitis and/or multiple sclerosis with VLA-4α-specific antibodies, as well as the combined teaching that viral infections can serve as triggers of relapse phases of multiple sclerosis as taught by Soilu-Hanninen et al. Or that viral infections can lead to encephalitis as taught by Planz et al. or that herpes viruses are associated with multiple sclerosis; treating patients populations encompassing symptomatic, asymptomatic and pediatric patients would have been targeted by the ordinary artisan at the time the invention was made. Also, given the viral component of encephalitis sclerosis; the ordinary artisan would have provide standard anti-inflammatory and antiviral treatment in addition to VLA-4α-specific antibodies at the time the invention was made to inhibit the T cell component of the inflammatory disease.

Applicant's arguments are not found persuasive.

7. No claim is allowed.

8. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

PHILLIP GAMBEL

Phillip Gambel, PhD.
Primary Examiner
Technology Center 1600
March 10, 2003